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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,481	02/10/2004	Scott A. Waldman	TJU0016-100/WAL_SCO.008	1053

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EXAMINER	
REDDIG, PETER J	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/775,481	WALDMAN ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64,65,68-103 and 132-144* is/are pending in the application.

4a) Of the above claim(s) *71,73,76-90,136-139 and 144* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64,65,68-70,72,74,75,91-103,132-135 and 140-143* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 July 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/16/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The response filed on August 3, 2007 to the restriction requirement of March 3, 2007 has been received. Applicant has elected Group VI, claims 64, 65, 68-103 for examination and the species intravenous, anti-ST antibodies and fragments thereof, metastasized colorectal cancer, and 5-fluorouracil without traverse. Applicants have added new claims 132-144. Upon review and reconsideration primary colorectal cancer will be rejoined for examination.

2. Claims 64, 65, 68-103 and 132-144 are pending.

3. Claims 71, 73, 76-90, 136-139, and 144 are hereby withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

4. Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132-135, and 140-143 as drawn to the species intravenous, anti-ST antibodies and fragments thereof, colorectal cancer, and 5-fluorouracil are currently under consideration.

Drawings

5. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: Figure 2d-f are not described in the brief description of the drawings. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required

corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

6. The disclosure is objected to because of the following informalities: There are two sections labeled Example 3, see p. 53 and 63.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132-135, and 140-143 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132-135, and 140-143 are indefinite because the term "substantially continuous infusion" in claims 64 and 65 renders the claims and their dependent claims indefinite. The terms "substantially continuous infusion" are not defined by the claim or the teachings of the specification and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. How is "substantially continuous infusion" achieved? Is the infusion continuous or is it not continuous? Is the claim drawn to someone being infused continuously until a cystostatic effect is observed, e.g. for weeks or months?

This rejection may be obviated by deleting the phrases "substantially continuous" and "per hour for a period of time sufficient" from claims 64 and 65.

Additionally, the term "substantially" in claims 64 and 65 is a relative term, which renders the claims and their dependent claims indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. At what point is a "substantially" continuous infusion achieved, after 1 hour, 1 day, or something else? Thus the metes and bounds of the claims cannot be determined.

Claim 68 is also indefinite because it cannot be determined if the claim is drawn to administering a therapeutic agent distinct from the ST ligand or just administering more of the ST receptor ligand. Is the ST receptor ligand not a therapeutic agent? Thus the metes and bounds of the claims cannot be determined.

Claim 133 is indefinite because it cannot be determined if the claim is drawn to conjugated pharmaceutical compositions, e.g. conjugating two solutions, a ST receptor binding moiety (i.e. the anti-ST receptor antibody) conjugated to a therapeutic agent, or composition in which the ST receptor binding moiety and therapeutic agent are not bound together.

This rejection may be obviated by amending claim 133 to . . . said therapeutic pharmaceutical composition comprising an ST receptor binding moiety conjugated to an active moiety, wherein said active moiety is a therapeutic agent.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132-135, and 140-143 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s)

contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to:

64. A method of inducing a cytostatic effect in a primary or metastasized colorectal cancer cell in an individual who has primary or metastasized colorectal cancer, said method comprising the step of: administering to said individual by substantially continuous infusion, a cytostatically effective amount of an ST receptor ligand, an anti-ST-receptor antibody or a fragment thereof, per hour for a period of time sufficient to have a therapeutic effect by the cytotoxic effect of the ST receptor ligand, an anti-ST-receptor antibody or a fragment thereof, wherein ST receptor ligand molecules bind to ST receptors on the surface of a primary or metastasized colorectal cancer cell in said individual and induces a cytostatic effect in said cells.

OR

65. A method of inhibiting the proliferation of a primary or metastasized colorectal cancer cell in an individual who primary or metastasized colorectal cancer, said method comprising the step of: administering to said individual by substantially continuous infusion, a cytostatically effective amount of an ST receptor ligand, an anti-ST-receptor antibody or a fragment thereof, per hour for a period of time sufficient to have a therapeutic effect by the cytostatic effect of the ST receptor ligand, an anti-ST-receptor antibody or a fragment thereof, wherein ST receptor ligand molecules bind to ST receptors on the surface of a primary or metastasized colorectal cancer cell in said individual and inhibits proliferation of said cells.

The specification teaches that heat-stable toxin (ST), which is a peptide produced by E. *coli,* can inhibit cell proliferation of cultured guanylyl cyclase C expressing T84 colon carcinoma cells in a CNG calcium channel dependent manner, see p. 53-59 and Figs. 1-4. The specification teaches that ST inhibited in colorectal cancer cells the release of matrix metalloproteinase 9, the organization of the actin cytoskeleton, and increased the adherence of colorectal cancer cells to type IV collagen, which are changes that could potentially inhibit the metastatic phenotype of colorectal cancer cells, see p. 63 and 64.

One cannot extrapolate the teachings of the specification to the enablement of the claims because no nexus has been established between administering an antibody to the ST receptor to an individual and inducing a cytostatic effect in primary or metastasized colorectal cancer cells in an individual or inhibiting proliferation of primary or metastasized colorectal cancer cells in an individual and because 1) the artifactual nature of cell culture systems is well known in the art and 2) the development of therapeutics for malignant disorders such as colorectal cancer is well known in the art to be unpredictable

1) As drawn to the artifactual nature of cell culture systems in particular, it is well known in the art that the characteristics of cultured cell lines generally differ significantly from the characteristics of the primary tumor. As discussed in Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4), it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer further teaches that when a normal or malignant cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment and thus transforms a cell from one that is stable and differentiated to one that is not. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, the art recognizes the problem of molecular artifacts associated with cell culture. For example, Drexler et al (Leukemia and

Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al. (Clin. Can. Res., 1998, 4:1797-1802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). More recently, Zips et al (In vivo, 2005, 19:1-7) specifically teaches that despite their importance for drug testing, *in vitro* methods are beset by pitfalls and inherent limitations (p. 3, col. 1). In particular the authors state that "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro,* a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and thereby, drug access to the tumor cells are not evenly distributed and in this fact consists an important source of heterogeneity in tumor response to drugs that does not exist *in vitro.* Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluations in animal tumor systems is essential" (p. 3, col. 2). Additionally Clark et al. (US Pat. App. Pub. 20060019256, January 2006) teach that "[a]lthough cell lines have led to remarkable advances in our understanding of the molecular and biochemical changes in cancer cells, their use in the identification of effective cancer therapies is somewhat limited. Cell lines are imperfect predictors of drug efficacy in de novo tumors. Several factors likely account for this deficiency. Cancer cell lines are selected from a sub-population of cancer cells that are specifically adapted to growth in tissue culture and the

biological and functional properties of these cell lines can change dramatically. Furthermore, cancer cells from only a minority of breast cancer tumors establish cell lines or xenograft tumors. The phenotypic and functional characteristics of these cell lines can change drastically relative to their properties in vivo. For example, the marker expression of both normal hematopoietic and leukemic tissue culture cells can change rapidly in tissue culture and often does not reflect that of the original stem cells from which they were derived. Even when conditions are devised to permit the proliferation of normal stem cells in culture, the conditions often promote self-renewal or differentiation in a way that prevents the stem cells in culture from recapitulating the hierarchy of cell populations that exist in vivo. Taken together, these observations suggest that the biological properties of cell lines can differ markedly from the cancer cells from which they were derived. This likely explains at least in part why the cell lines often are poor predictors of a drug's efficacy in the clinic," see para. 0109.

Thus, based on the cell culture data presented in the specification, in the absence of data demonstrating that antibody directed against the ST receptor can induce a cytostatic effect in primary or metastasized colorectal cancer cells in an individual or inhibit proliferation of primary or metastasized colorectal cancer cells in an individual in an appropriate *in vivo* model system, no one of skill in the art would believe it more likely than not that the invention would function as claimed, that is inducing a cytostatic effect in primary or metastasized colorectal cancer cells in an individual or inhibiting proliferation of primary or metastasized colorectal cancer cells in an individual, based only on the cell culture data provided.

2) As drawn to the unpredictability of drug development for malignant disorders such as cancer, it is well known that the art of anticancer drug discovery for cancer therapy is highly

unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Furthermore, Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Additionally, Young et al. (US Patent Application Pub. 20040180002, September 15, 2004) teach that there have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. Young et al. teach that It was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches "to date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate and stomach cancers" (para 0011 of the published application). Thus, it is clear that the art recognizes that it could not be predicted, nor would it be expected that based only on the *in vitro* data presented in the specification that it would be more likely than not that the claimed method could be effectively used for inducing a cytostatic effect in primary or metastasized colorectal cancer cells in an individual or inhibiting proliferation of primary or metastasized colorectal cancer cells in an individual.

Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col. 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col. 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col. 2). It is clear that based on the state of the art, in the absence of *in vivo* experimental evidence, no one skilled in the art would accept the assertion that an antibody directed against the ST receptor could predictably be used in a method of inducing a cytostatic effect in primary or metastasized colorectal cancer cells in an individual or inhibiting proliferation of primary or metastasized colorectal cancer cells in an individual. In addition, anti-tumor antibodies must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the cancer and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the antibody. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy.

The antibody may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life of the antibody. In addition, the antibody may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where it has no effect, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established.

Given the above, in the absence of *in vivo* experimental data demonstrating induction of a cytostatic effect in primary or metastasized colorectal cancer cells in an individual or inhibition of proliferation of primary or metastasized colorectal cancer cells in an individual with an antibody against the ST receptor or fragment thereof, one of skill in the art could not predict that the invention will function as claimed with a reasonable expectation of success

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the stare of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as claimed

based only on the information in the specification and that known in the art at the time the invention was made. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

9. If Applicants were able to overcome the rejections set forth above under 35 U.S.C. 112, first paragraph, claims 74 and 134 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the methods of claims 64, 65, or 132 using an anti-ST receptor antibody, does not reasonably provide enablement for the methods of claims 64, 65, or 132 using **a fragment** of an anti-ST receptor antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to:

74. The method of claim 64 or 65 wherein said ST receptor ligand is an anti-ST receptor antibody or a fragment thereof.

134. The method of claim 133 wherein said ST receptor ligand is an anti-ST receptor antibody or a fragment thereof.

The specification teaches as set forth above.

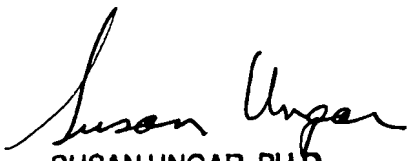
The teaching of the specification cannot be reasonably extrapolated to enable the scope of the claims because one of skill in the art would not predict that any fragment of an anti-ST receptor antibody would be useful in the claimed methods. Fragments of antibodies include not only the antigen-binding region but also the Fc portion (Roitt et al., Immunology, Third Edition (Mosby, London England) p. 1.7). One of skill in the art would expect that only antigen-binding fragments of the an anti-ST receptor antibody antibody would be useful inducing a cytostatic effect or inhibiting the proliferation of primary or metastasized colorectal cancer cells. Thus, one of skill in the art could not predict that the invention would function as claimed. Therefore, practice of the invention would require undue experimentation

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Peter J. Reddig
Examiner
Art Unit 1642

PJR